Strengthening our knowledge in Spondylarthritides: Focusing on Ankylosing Spondylitis and Psoriatic Arthritis

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Outline

Spondyloarthritis: definition and prevalence

Ankylosing spondylitis and psoriatic arthritis

Clinical features

Pathophysiology of SpA

Diagnosis and treatment

Comorbidities and disease load
Spondyloarthritis (SpA) can have diverse symptoms and be difficult to identify.

**Musculoskeletal symptoms**
- Joint pain in fingers or toes
- Chronic back pain
- Enthesitis
- Dactylitis

**Extra-articular symptoms**
- Uveitis
- Psoriasis

**Risk factors**
- Recent genitourinary infection
- Family history of spondyloarthritis
- Family history of psoriasis

**Identifying and referring Spondyloarthritis**

**Suspected axial spondyloarthritis**
- Low back pain
- Started before age 45
- Lasting longer than 3 months

Assess for referral criteria:
- Low back pain that started before the age of 35 years
- Waking during the second half of the night because of symptoms
- A first-degree relative with spondyloarthritis
- Improvement within 48 hours of taking non-steroidal anti-inflammatory drugs (NSAIDs)
- Improvement with movement

**Extra referral criteria**
- 2 or fewer referral criteria
- Exactly 3 referral criteria
- 4+ referral criteria

**HLA-B27 test**
- Negative
- Positive

**Specialist referral**
- Refer to a rheumatologist for specialist diagnostic assessment
- Advise repeat assessments if new signs, symptoms or risk factors develop

**Suspected psoriatic arthritis or peripheral spondyloarthritis**
- Dactylitis
- Inflammation of fingers or toes

**Suspected new-onset inflammatory arthritis**
- No apparent mechanical cause
- Enthesitis
- Inflammation of entheses, often in the heel
- Persistent or multiple sites
- A concurrent or historic condition

**Special conditions**
- Back pain without apparent cause
- Current or past uveitis
- Psoriasis
- Gastrointestinal
- Genitourinary infection
- Inflammatory bowel disease
- A first-degree relative with spondyloarthritis or psoriasis

**Other conditions**
- Usually managed in primary care
- Acute calcium pyrophosphate (CPP) arthritis
- Gout
- Rheumatoid arthritis
- No additional features
Spondyloarthritis

• Spondyloarthritis (SpA) is a group of inflammatory rheumatic diseases comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, undifferentiated SpA and SpA associated with inflammatory bowel disease.

• These interrelated disorders share clinical features, run in families and are associated with HLA-B27.

• SpA can also be characterized as axial or peripheral according to predominant articular features at clinical presentation.

• Axial SpA involves spondylitis and sacroiliitis, whereas the main features of peripheral SpA are peripheral arthritis, enthesitis and dactylitis.

Οι οροαρνητικές αρθρίτιδες χαρακτηρίζονται από διαβρώσεις και οστεοπαραγωγή.

- Ρευματοειδής αρθρίτιδα: Διαβρώσεις μεταταρσοφαλαγγικών
- Ψωριασική αρθρίτιδα: Διαβρώσεις αλλά και εξωαρθρική περιοστίτιδα
Features of the Spondyloarthritis

van Tubergen, A. Nat. Rev. Rheumatol. 11, 110–118 (2015);
ASAS classification criteria for axial and peripheral SpA

van Tubergen, A. Nat. Rev. Rheumatol. 11, 110–118 (2015);
Disorders share distinctive clinical, radiographic, and genetic features:

- Rheumatic diseases characterized by **sacroiliitis, spondylitis, enthesitis, dactylitis** and **synovitis**
- Extra-articular manifestations (uvea, gut, skin)
- Strong association with HLA B27
- Positive family history of SpA
Diffuse idiopathic skeletal hyperostosis vs sPA
Diffuse idiopathic skeletal hyperostosis vs sPA
AS Has a Multitude of Effects on the Body

AS, ankylosing spondylitis; CV, cardiovascular.

PsA Impacts Both Physical and Emotional Well-being

PsA, psoriatic arthritis
The prevalence of SpA ranged from 0.20% (95% CI 0.00–0.66) in South-East Asia to 1.61% (95% CI 1.27–2.00) in Northern Arctic communities.

The following characteristics were significantly associated with variation in prevalence of SpA:
- proportion of females
- mean age of the sample
- geographic area and setting
- year of data collection
- case finding and case ascertainment (methodologic characteristics)

The prevalence of SpA has been reported higher in more recent studies (year of data collection from 2000 onwards).
The prevalence of AS ranges ~ 0,5-1,9% globally.

Additionally there is some gender disparity within AS, with reported gender ratios of around 2:1 male to female.

There were also differences between the sexes regarding some AS-related clinical manifestations. I.e. anterior uveitis was more common in men, and peripheral arthritis and psoriasis were more common in women.

AS usually initially presents during the second and third decade of life, and rarely after the age of 45 years.

There is a considerable delay (8 to 15 years) in obtaining a definitive diagnosis from a specialist.

AS prevalence correlates with the prevalence of HLA-B27.
Prevalence of AS in Greece

SpA was diagnosed in 39 individuals (32 males and 7 females) with a mean age of 46.18 ± 14.75 years (Table I). Thus, the crude prevalence of SpA (8740 responders) was 0.45% (95% CI: 0.31–0.59), while in the total target adult population (14,233 subjects) the prevalence\textsubscript{asa} of SpA was 0.49% (95% CI: 0.38–0.60). The prevalence\textsubscript{asa} of SpA was significantly higher among males (0.83%) compared to females (0.15%) in the total

The SpA group consisted of patients with AS (50.7%), PsA (34.8%), ReA (8.7%), and uSpA (5.8%). The most common disease was AS followed by PsA with a prevalence\textsubscript{asa} of 0.24% (95% CI: 0.16–0.32) and 0.17% (95% CI: 0.10–0.24), respectively. The prevalence\textsubscript{asa} was significantly higher ($p \leq 0.001$) in males (0.43% in AS and 0.29 in PsA) compared to females (0.07% in AS and 0.06% in PsA), with a sex ratio of 6.1:1 in AS and 4.8:1 in PsA. The prevalence\textsubscript{asa} of PsA

SpA with axial involvement (sacroiliitis and/or inflammatory spinal pain) in the study population was observed at a prevalence of 0.34% (95% CI: 0.24–0.44). Sacroiliitis was recorded in all AS and in 39.8% of PsA patients, while the percentage of patients who had had (past and/or current) peripheral involvement was 59.5 of AS and 95.5 of PsA cases. Peripheral arthritis in PsA showed a pattern of asymmetric oligoarthritis in 40.6% patients, of symmetric polyarthritis (rheumatoid-like) in 25.4%, and of distal interphalangeal joints in 29.6%.
The prevalence of psoriatic arthritis among patients with psoriasis increased significantly on the basis of the body surface area involved with psoriasis.

The development of PsA appears to occur at a constant rate during each year following psoriasis diagnosis, resulting in a steady increase in PsA prevalence.
Outline

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Ankylosing spondylitis and psoriatic arthritis

Clinical features

Pathophysiology of SpA

Diagnosis and treatment

Comorbidities and disease load
Ankylosing spondylitis (AS)

Table 1. Current and Classic Classifications of Spondyloarthritis.*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current classifications</strong></td>
<td></td>
</tr>
<tr>
<td>Axial spondyloarthritis</td>
<td>With radiographic sacroiliitis</td>
</tr>
<tr>
<td></td>
<td>Without radiographic sacroiliitis</td>
</tr>
<tr>
<td></td>
<td>Sacroiliitis on MRI</td>
</tr>
<tr>
<td></td>
<td>HLA-B27 positivity plus clinical criteria</td>
</tr>
<tr>
<td>Peripheral spondyloarthritis</td>
<td>With psoriasis</td>
</tr>
<tr>
<td></td>
<td>With inflammatory bowel disease (Crohn’s disease or ulcerative colitis)</td>
</tr>
<tr>
<td></td>
<td>With preceding infection</td>
</tr>
<tr>
<td></td>
<td>Without psoriasis or inflammatory bowel disease or preceding infection</td>
</tr>
<tr>
<td><strong>Classic classifications</strong></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td></td>
</tr>
<tr>
<td>Reactive arthritis (infection-associated arthritis)</td>
<td></td>
</tr>
<tr>
<td>Psoriatic spondyloarthritis</td>
<td>Predominantly peripheral</td>
</tr>
<tr>
<td></td>
<td>Predominantly axial</td>
</tr>
<tr>
<td>Enteropathic spondyloarthritis (associated with inflammatory bowel disease)</td>
<td>Predominantly peripheral</td>
</tr>
<tr>
<td></td>
<td>Predominantly axial</td>
</tr>
<tr>
<td>Juvenile-onset spondyloarthritis (enthesitis-related juvenile idiopathic arthritis)</td>
<td>Undifferentiated spondyloarthritis</td>
</tr>
</tbody>
</table>

* Current classifications are adapted from the Assessment of SpondyloArthritis International Society (ASAS) by Rudwaleit et al.™ MRI denotes magnetic resonance imaging.
Σκελετός με αλλοιώσεις ΑΣ που περιγράφηκε από τον Bernard Connor το 1695
AS classification

- AS is axial SpA with significant X-ray changes manifested through sacroiliitis, meeting the modified New York criteria (1984) for AS \(^1\,^2\)

\[\text{Non-radiographic stage} \quad \text{Radiographic stage}\]

- Back pain
  - Sacroiliitis on MRI
- Back pain
  - Radiographic sacroiliitis
- Back pain
  - Syndesmophytes

**Modified New York Criteria 1984**

Time (years)


ASAS, Assessment of SpondyloArthritis internati

Clinical features of AS

Clinical features
- Long-term disease that causes inflammation of joints between spinal bones and the joints between the spine and pelvis
- Eventually causes affected spinal bones to fuse together
- Clinical features include inflammation, structural damage, and repair
- Negative impact on QoL and psychological well-being
- Likely related to genetic and environmental factors
- It is majorly diagnosed in young men

Laboratory features
- No laboratory test is diagnostic of AS
- HLA-B27
  - Presence of the gene HLA-B27 is a strong predictor of axial SpA
  - Approximately 80-95% of patients with AS are HLA-B27 positive
- C-reactive protein (CRP)
  - Levels of CRP increase in response to inflammation and may be associated with structural changes in the spine associated with axial SpA
- Erythrocyte sedimentation rate (ESR)
  - A measure of inflammation
  - Commonly used in the assessment of RA and other inflammatory disorders


HLA, human leukocyte antigen; RA, rheumatoid arthritis
Inflammatory vs mechanical back pain

Mechanical back pain:
- is much more frequent
- refers to pain that arises from an injury to a specific structure within the spine
- has usually a full recovery within the first few weeks
- has morning stiffness <30 min
- is improved with rest

Table 2. Characteristics of Inflammatory Back Pain.*

<table>
<thead>
<tr>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, &lt;45 yr</td>
</tr>
<tr>
<td>Duration, &gt;3 mo</td>
</tr>
<tr>
<td>Insidious onset</td>
</tr>
<tr>
<td>Morning stiffness &gt;30 min</td>
</tr>
<tr>
<td>Improvement with exercise</td>
</tr>
<tr>
<td>No improvement with rest</td>
</tr>
<tr>
<td>Awaking from pain, especially during second half of night, with improvement on arising</td>
</tr>
<tr>
<td>Alternating buttock pain</td>
</tr>
</tbody>
</table>

* The presence of two or more of these features should arouse suspicion for inflammatory back pain, and the presence of four or more features can be considered diagnostic. The sensitivity of inflammatory back pain for the diagnosis of axial spondyloarthritis is 70 to 80%. The specificity varies, depending on the population being studied.5,9

New bone formation progressively leads to ankylosis

Clinical features of PsA

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Explanation</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current psoriasis</td>
<td>Current psoriatic skin or scalp disease as judged by a dermatologist or rheumatologist</td>
<td>2</td>
</tr>
<tr>
<td>Personal history of psoriasis</td>
<td>History of psoriasis according to the patient or a family doctor, dermatologist, or rheumatologist</td>
<td>1</td>
</tr>
<tr>
<td>Family history of psoriasis</td>
<td>History of psoriasis in a first- or second-degree relative according to the patient</td>
<td>1</td>
</tr>
<tr>
<td>Psoriatic nail dystrophy</td>
<td>Typical psoriatic nail dystrophy (e.g., onycholysis, pitting, or hyperkeratosis) according to observation during current physical examination</td>
<td>1</td>
</tr>
<tr>
<td>Negative test for rheumatoid factor</td>
<td>Based on reference range at local laboratory; any testing method except latex, with preference for ELISA or nephelometry</td>
<td>1</td>
</tr>
<tr>
<td>Dactylitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current dactylitis</td>
<td>Swelling of an entire digit according to observation on current physical examination</td>
<td>1</td>
</tr>
<tr>
<td>History of dactylitis</td>
<td>According to a rheumatologist</td>
<td>1</td>
</tr>
<tr>
<td>Radiographic evidence of juxtaarticular new bone formation</td>
<td>Ill-defined ossification near joint margins (excluding osteophyte formation) on plain radiographs of hand or foot</td>
<td>1</td>
</tr>
</tbody>
</table>

*Psoriatic arthritis is considered to be present in patients with inflammatory musculoskeletal disease (disease involving the joint, spine, or enthesis) whose score on the five criteria listed in the table totals at least three points; the “evidence of psoriasis” criterion can account for either one point or two points. The criteria have a specificity of 98.7% and a sensitivity of 91.4%. ELISA denotes enzyme-linked immunosorbent assay.

Clinical manifestations of PsA

Psoriasis
Nail psoriasis

Arthritis

Enthesitis
35%

Dactylitis
35%

Axial involvement (40%)

Peripheral involvement (60-90%)

Polyarthritis (RA-like)
25% → 65%

Oligoarthritis
65% → 25%

Erosions of Distal phalanx (OA-like)
10-20%

Erosive arthritis <1%

Dactylitis 35%

Enthesitis 35%
Clinical features

- Peripheral arthritis
- Achilles tendinopathy
- Dactylitis
- Anterior Uveitis
- Crohn’s disease
- Psoriasis
Outline

Spondyloarthritis: definition and prevalence

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Comorbidities and disease load
Mechanical stress can induce an inflammatory response at the enthesis in genetically susceptible individuals and/or those under microbial stress. 

- Mechanical stress is a key trigger for enthesitis in AS and PsA.
Enthesitis differentiates AS and PsA from rheumatoid arthritis

• Primary synovial membrane disease vs. entheseal disease with secondary synovial membrane involvement
• Aids differential diagnosis of AS / PsA vs. rheumatoid arthritis
Pathophysiology of enthesitis

APK: antigen-presenting cells, IL-23R: receptor for IL-23 ROR-γt: RAR-related orphan receptor γ, which RAR = retinoic acid receptor
IL-17A is an amplifier of enthesitis, leading to irreversible structural damage

Mechanosensation & immune activation

- Triggers
  - Mechanical stress
  - Disturbed barrier function
  - Infections

<table>
<thead>
<tr>
<th>Triggers</th>
<th>PGE2</th>
<th>Vasodilation</th>
<th>IL-17</th>
<th>Neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disturbed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Innate inflammatory response

- γδT cells
- ILC3
- IL-17
- TNF

- Neutrophils
- MSCs
- IL-22

Mesenchymal proliferation

- γδT cells
- ILC3
- IL-17
- MSCs
- BMPs
- Osteoblast
- Hypertrophic chondrocyte

New bone formation

- Hedgehog
- PTHrP
- Wnts
- BMPs

ILC= innate lymphoid cells

- ILC1→IFN-γ
- ILC2→IL-5, IL-6, IL-13
- ILC3→IL-17, IL-22

BMP, bone morphogenic proteins; IL-22, interleukin 22; PTHrP, parathyroid hormone related-peptide; MSC, mesenchymal stem cell

IL-17 stimulates osteoblast to express RANKL which stimulates Osteoclast to destroy the bone.
Pathogenic Mechanisms in Axial Spondyloarthritis

Pathogenic Pathways in Ankylosing Spondylitis

Genetic predispositions
- HLA-B (B*27:05, B*08:01..)
- HLA-C (C*01:02, C*06:02..)

Environmental triggers
- Mechanical stress, infection, injury...

Skin inflammation, gut inflammation, joint inflammation...

Inflammatory response by macrophages, synovial fibroblasts, nociceptors...

- IL-23, IL-1β, IL-6, TGF-β
- Th17, Tc17, γδT, ILC3, Th22

MCSF, TNF-α, RANKL

Cytokines

Cells

TNF-α

? Osteoblast

New bone formation

Bone erosion

Osteoclast
<table>
<thead>
<tr>
<th>Outline</th>
</tr>
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<tbody>
<tr>
<td>Spondyloarthritis: definition and prevalence</td>
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<td>Ankylosing spondylitis and psoriatic arthritis</td>
</tr>
<tr>
<td>Clinical features</td>
</tr>
<tr>
<td>Pathophysiology of SpA</td>
</tr>
<tr>
<td>Diagnosis and treatment</td>
</tr>
<tr>
<td>Comorbidities and disease load</td>
</tr>
</tbody>
</table>
Delay in diagnosis in AS

Currently, there is a long delay, from 5 to 10 years, between the first occurrence of AS symptoms and a diagnosis of AS.

Two major reasons can be named for such a delay:
(a) There is certainly a low awareness of AS among non-rheumatologists and it can be seen as a major challenge for any physician in primary care to think of and to identify patients with inflammatory spine disease among the large group of patients with chronic back pain, most often of another origin.
(b) Radiographic sacroiliitis grade 2 bilaterally or grade 3 or 4 unilaterally is usually a requirement for making the diagnosis of AS according to the modified New York criteria.

The delay in diagnosis and the worsening of AS symptoms leads to physical, emotional and disease-related work disability.
### Delay in diagnosis of AS

#### TABLE 1. Characteristics of AS patients diagnosed during the period 1983–2002 in northwest Greece

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>113</td>
</tr>
<tr>
<td>Men/women</td>
<td>93/20</td>
</tr>
<tr>
<td>Age at diagnosis (yr): mean (s.d.) [range]</td>
<td>39.8 (11.5) [16–76]</td>
</tr>
<tr>
<td>Age at disease onset (yr): mean (s.d.) [range]</td>
<td>30.5 (10.7) [16–69]</td>
</tr>
<tr>
<td>HLA-B27-positive</td>
<td>91 (80.5)</td>
</tr>
<tr>
<td>Axial involvement</td>
<td>113 (100%)</td>
</tr>
<tr>
<td>Peripheral joints</td>
<td>40 (35.4%)</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td>15 (13.3%)</td>
</tr>
</tbody>
</table>
## Diagnosis of AS: Indexes that are commonly used in clinical trials

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Axial skeleton</th>
<th>Peripheral skeleton</th>
<th>Enthesitis</th>
<th>Radiographic findings</th>
<th>Functionality/Quality of life</th>
<th>Mobility</th>
<th>Pain</th>
<th>Dactylitis</th>
<th>Inflammation indexes</th>
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<tbody>
<tr>
<td>BASDAI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>BASMI</td>
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<td>BASFI</td>
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<td></td>
<td></td>
<td>✓</td>
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<tr>
<td>MEI/MASES/SPARCC/LEI</td>
<td></td>
<td>✓</td>
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<td></td>
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<tr>
<td>ASAS 20/40</td>
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<tr>
<td>ASAS 5/6</td>
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<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>ASDAS</td>
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<td>HAQ</td>
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<td>SF-36</td>
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<td>✓</td>
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<tr>
<td>mSASSS</td>
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<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Progression of psoriatic arthritis

Psoriasis onset
(30% of pts will be diagnosed with PsA)

At least 1 erosion
47%

Erosion of at least 5 joints
55%

Severe pain and disability

Increased mortality due to CVD

20%: Severe/Erosive disease

Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis

Muhammad Haroon, Phil Gallagher, Oliver FitzGerald

**Rheumatologist’s diagnosis**

- < 6 months: 30%
- < 1 year: 53%
- < 2 years: 71%

**Delay in diagnosis > 6 months**

- Erosions: 4.25
- Functional disability (HAQ): 2.2
- No. of DMARDs/TNFi failures: 1.47
- DMARD/TNFi free: 0.42

Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis after a mean of 10 years of follow-up.

Clinical features recorded as percent, unless otherwise stated

CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; OR, odds ratio

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosions</td>
<td>4.6 (2.5–8.2)</td>
</tr>
<tr>
<td>Number of deformed joints (score)</td>
<td>1.1 (1.0–1.1)</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>2.3 (1.2–4.4)</td>
</tr>
<tr>
<td>Arthritis mutilans</td>
<td>10.6 (1.4–80.6)</td>
</tr>
<tr>
<td>Functional disability (HAQ score)</td>
<td>2.2 (1.3–3.6)</td>
</tr>
<tr>
<td>DMARD/anti-TNF free</td>
<td>0.4 (0.2–0.9)</td>
</tr>
</tbody>
</table>

2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis

Désirée van der Heijde,¹ Joachim Sieper,² Walter P Maksymowycz,³ Maxime Dougados,⁴ Rubén Burgos-Vargas,⁵ Robert Landewé,⁶,⁷ Martin Rudwaleit,² Jürgen Braun⁸; for the Assessment of SpondyloArthritis international Society

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**Treatment**

<table>
<thead>
<tr>
<th>Pre-radiographic stage (Undifferentiated axial SpA)</th>
<th>Radiographic stage (Ankylosing spondylitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain (MRI: active sacroiliitis)</td>
<td>Back pain Radiographic sacroiliitis</td>
</tr>
<tr>
<td></td>
<td>Back pain Syndesmophytes</td>
</tr>
</tbody>
</table>

Time (years)
Spondyloarthritis—Current treatments

- **NSAIDs**
- **DMARDs:**
  - Methotrexate
  - Sulfasalazine
  - Cyclosporine (?)
  - Leflunomide
  - TNF-α inhibitors
  - Ustekinumab (anti-p14, IL-12/IL-23)
  - Apremilast (ts DMARD)
  - Secukinumab (anti-IL-17A)

New compounds in spondyloarthritis

Table 1. Published efficacy data on new compounds in spondyloarthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Disease subtype</th>
<th>Approved</th>
<th>Highest phase published</th>
<th>Study name</th>
<th>Primary endpoint met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab</td>
<td>anti-p14 (IL-23)</td>
<td>PsA</td>
<td>Yes</td>
<td>III</td>
<td>PSUMMIT I/II (Kavanagh et al., 2016; McInnes et al., 2013)</td>
<td>Yes</td>
</tr>
<tr>
<td>Apremilast</td>
<td>PDE-4 inhibitor</td>
<td>PsA</td>
<td>No</td>
<td>II</td>
<td>TOPAS (Podubryy et al., 2014) (Open-label proof of concept)</td>
<td>Yes</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>anti-IL-17A</td>
<td>PsA</td>
<td>Yes</td>
<td>III</td>
<td>PALACE I/II/III (Kavanagh et al., 2014; Schett et al., 2012)</td>
<td>Yes</td>
</tr>
<tr>
<td>AS/ nrAxSpA</td>
<td>PsA</td>
<td>Yes</td>
<td>III</td>
<td>Measure I/II (Baeten et al., 2015)</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Ixeizumab</td>
<td>anti-IL-17A</td>
<td>PsA</td>
<td>No</td>
<td>III</td>
<td>SPIRIT-P 1 and 2 (Mease et al., 2016; Nash et al., 2017)</td>
<td>Yes</td>
</tr>
<tr>
<td>AS</td>
<td>PsA</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>ASTRAEA (Mease et al., 2017)</td>
<td>Yes</td>
</tr>
<tr>
<td>Abatacept</td>
<td>CTLA-4</td>
<td>PsA</td>
<td>yes</td>
<td>III</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IL, interleukin; NrAxSpA, nonradiographical axial spondyloarthritis; PDE, phosphodiesterase; PSA, psoriatic arthritis; TOPAS, Toronto Psoriatic Arthritis Screen.
Efficacy of biologics and other novel drugs in SpA and other chronic inflammatory diseases

<table>
<thead>
<tr>
<th>Target</th>
<th>Therapeutic agent</th>
<th>Efficacy Axial SpA</th>
<th>PsA</th>
<th>Psoriasis</th>
<th>Crohn’s disease</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>Adalimumab (monoclonal antibody to TNF)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Certolizumab pegol (monoclonal antibody to TNF)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Etanercept (fusion protein against TNF)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Golimumab (monoclonal antibody to TNF)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Infliximab (monoclonal antibody to TNF)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IL-1</td>
<td>Anakinra (IL-1 receptor antagonist)</td>
<td>-?</td>
<td>+?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>B cells</td>
<td>Rituximab (monoclonal antibody to CD20)</td>
<td>-?</td>
<td>+?</td>
<td>?</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>T cells</td>
<td>Abatacept (inhibitor of T-cell co-stimulation)</td>
<td>-?</td>
<td>-</td>
<td>-?</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IL-6</td>
<td>Tocilizumab (monoclonal antibody to IL-6 receptor)</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>Sarilumab (monoclonal antibody to IL-6 receptor)</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Efficacy of biologics and other novel drugs in SpA and other chronic inflammatory diseases

<table>
<thead>
<tr>
<th>Target</th>
<th>Therapeutic agent</th>
<th>Efficacy Axial SpA*</th>
<th>PsA</th>
<th>Psoriasis</th>
<th>Crohn's disease</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17</td>
<td>Secukinumab (monoclonal antibody to IL-17)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab (monoclonal antibody to IL-17)</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Brodalumab (monoclonal antibody to IL-17 receptor)</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>IL-12 and IL-23</td>
<td>Ustekinumab (monoclonal antibody to IL-12 and IL-23)</td>
<td>+?</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Gusekumab (monoclonal antibody to IL-12)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tildrakizumab (monoclonal antibody to IL-23)</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>BI 853066 (monoclonal antibody to IL-23)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PDE4</td>
<td>Apremilast (PDE4 inhibitor, small molecule)</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>JAK</td>
<td>Tofacitinib (JAK1 and JAK3 inhibitor, small molecule)</td>
<td>-?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>-</td>
</tr>
</tbody>
</table>

*+, efficacy shown in at least one randomized controlled trial; ?, some data from pilot or proof-of-concept trials indicate a positive effect; -, lack of efficacy shown in at least one randomized controlled trial; ?, no conclusive data available regarding efficacy; JAK, Janus kinase; PDE4, 3',5'-cyclic AMP phosphodiesterase-4; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis. *Data on efficacy in the two subgroups of axial SpA (nonradiographic axial SpA and ankylosing spondylitis) exist only for adalimumab, certolizumab pegol, etanercept and golimumab; other drugs for which efficacy data are available were investigated in ankylosing spondylitis only.

Outline

- Spondyloarthritis: definition and prevalence
  - Ankylosing spondylitis and psoriatic arthritis
  - Clinical features
  - Pathophysiology of SpA
  - Diagnosis and treatment
  - Comorbidities and disease load
Prevalence of evaluated comorbidities in the 3984 patients with spondyloarthritis
Withdrawal from work due to disease-related disability in patients with AS in the period before biologic treatments

Table 1  Age and sex adjusted risk ratios (95% CI) for withdrawal from labour force in ankylosing spondylitis (AS) compared with the general Dutch population

<table>
<thead>
<tr>
<th></th>
<th>Male AS patients</th>
<th></th>
<th></th>
<th>Female AS patients</th>
<th></th>
<th></th>
<th>All AS patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>RR (95% CI)</td>
<td>Observed</td>
<td>Expected</td>
<td>RR (95% CI)</td>
<td>Observed</td>
<td>Expected</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>&lt;25 years</td>
<td>3</td>
<td>0.36</td>
<td>8.3 (1.7 to 24.3)</td>
<td>1</td>
<td>0.24</td>
<td>4.2 (0.1 to 23.3)</td>
<td>4</td>
<td>0.59</td>
<td>6.7 (1.8 to 17.1)</td>
</tr>
<tr>
<td>25–34 years</td>
<td>31</td>
<td>5.28</td>
<td>5.9 (4.0 to 8.3)</td>
<td>9</td>
<td>4.66</td>
<td>1.9 (0.9 to 3.7)</td>
<td>40</td>
<td>9.94</td>
<td>4.0 (2.9 to 5.5)</td>
</tr>
<tr>
<td>35–44 years</td>
<td>27</td>
<td>7.52</td>
<td>3.6 (2.4 to 5.2)</td>
<td>12</td>
<td>5.53</td>
<td>2.2 (1.1 to 3.8)</td>
<td>39</td>
<td>13.05</td>
<td>3.0 (2.1 to 4.1)</td>
</tr>
<tr>
<td>45–54 years</td>
<td>23</td>
<td>8.19</td>
<td>2.8 (1.8 to 4.2)</td>
<td>6</td>
<td>2.58</td>
<td>2.3 (0.4 to 5.1)</td>
<td>29</td>
<td>10.77</td>
<td>2.7 (1.8 to 3.9)</td>
</tr>
<tr>
<td>≥55 years</td>
<td>2</td>
<td>2.03</td>
<td>0.98 (0.1 to 3.6)</td>
<td>0</td>
<td>0.30</td>
<td>---</td>
<td>2</td>
<td>2.33</td>
<td>0.85 (0.1 to 3.1)</td>
</tr>
<tr>
<td>All patients</td>
<td>86</td>
<td>23.38</td>
<td>3.7 (2.9 to 4.4)</td>
<td>28</td>
<td>13.32</td>
<td>2.1 (1.4 to 3.0)</td>
<td>114</td>
<td>36.69</td>
<td>3.1 (2.5 to 3.7)</td>
</tr>
</tbody>
</table>

RR = standardised risk ratios.
Efficacy and Safety of secukinumab (anti-IL-17A) up to 4 years of treatment
The MEASURE Clinical Trial Program:
Assessment of Secukinumab in AS

<table>
<thead>
<tr>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td>Q2</td>
<td>Q3</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
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<tr>
<td>Q3</td>
<td>Q1</td>
<td>Q2</td>
<td>Q4</td>
<td>Q4</td>
</tr>
<tr>
<td>Q4</td>
<td>Q4</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
</tr>
</tbody>
</table>

**MEASURE 1 – N = 371**
i.v. loading (10 mg/kg) → s.c. maintenance dosing (75 or 150 mg)

**Extension Study**

**MEASURE 2 – N = 219**
s.c. loading (75 or 150 mg) → s.c. maintenance dosing (75 or 150 mg)
Pre-filled syringe

**MEASURE 3 – N = 226**
i.v. loading (10 mg/kg) → s.c. maintenance dosing (150 or 300 mg)

**MEASURE 4 – N = 350**
s.c. 150 mg with or without s.c. loading (Pre-filled syringe)

Clinicaltrials.gov: NCT01358175 (MEASURE 1); NCT01649275 (MEASURE 2); NCT02008916 (MEASURE 3); NCT02159053 (MEASURE 4).

MEASURE 1 is a 2-year study with 3-year extension study; MEASURE 2 is a 5-year study; MEASURE 3 is a 3-year study; MEASURE 4 is a 2-year study. The primary endpoint for all studies is at Week 16.
i.v., intravenous; s.c., subcutaneous.
Secukinumab 150 mg Provided Sustained ASAS20/ASAS40 Responses Through 4 Years

Secukinumab 10 mg/kg i.v. → 150 mg s.c.

- Observed data
- Imputed data (N = 87)

% Responders

ASAS20

- Observed data through Week 208
- Imputed data through Week 208

ASAS40

- Observed data through Week 208
- Imputed data through Week 208

Obs n = 87

Weeks

ASAS, Assessment of Spondyloarthritis International Society; n, number of pts evaluated in the treatment group; N, total number of pts in the extension trial; Obs, observed data. Solid lines represent observed data through Week 208. Dashed lines represent multiple imputation data through Week 208.
Secukinumab 150 mg Provided Sustained Improvement in BASDAI, BASFI and BASMI Through 4 Years

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; n, number of pts evaluated in the treatment group; Obs, observed data. Observed data through Week 208.
The FUTURE Clinical Trial Program:
Assessment of Secukinumab in PsA

<table>
<thead>
<tr>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FUTURE 1 – N = 606**
- i.v. loading (10 mg/kg) ➔ s.c. maintenance dosing (75 and 150 mg)

**FUTURE 2 – N = 397**
- s.c. loading (75, 150, and 300 mg) ➔ s.c. maintenance dosing (75, 150, and 300 mg)
  - Pre-filled syringe

**FUTURE 3 – N = 414**
- s.c. loading (150 and 300 mg) ➔ s.c. maintenance dosing (150 and 300 mg)
  - Autoinjector

**FUTURE 4 – N = 341**
- s.c 150 mg with or without s.c. loading
  - Pre-filled syringe

**FUTURE 5 – N = 996**
- s.c 150 mg and 300 mg with or without s.c. loading (Pre-filled syringe)

FUTURE 1 is a 2-year study (primary endpoint at Week 24) with 3 year extension study; FUTURE 2 is a 5 year study (primary endpoint at Week 24); FUTURE 3 is a 3 year study; FUTURE 4 is a 2 year study (primary endpoint at Week 16); FUTURE 5 is a 2 year study (primary endpoint at Week 24).

i.v., intravenous; s.c., subcutaneous.
Sustained Improvement in ACR20/50/70 Responses Through 3 years (Overall Population)

Overall (Multiple Imputation)

- ACR20: 76.8%
- ACR50: 54.9%
- ACR70: 32.9%

Anti–TNF-naive (Observed Data)

- ACR20: 81.0%
- ACR50: 62.9%
- ACR70: 38.8%

Anti–TNF-IR (Observed Data)

- ACR20: 61.5%
- ACR50: 35.9%
- ACR70: 17.9%

Secukinumab IV→150 mg

Secukinumab Provided Sustained Resolution of Dactylitis and Enthesitis Through 3 years (Overall Population)

Resolution of Dactylitis

<table>
<thead>
<tr>
<th>Week 52</th>
<th>Week 104</th>
<th>Week 156</th>
</tr>
</thead>
<tbody>
<tr>
<td>82.0</td>
<td>86.5</td>
<td>88.1</td>
</tr>
<tr>
<td>84.4</td>
<td>88.6</td>
<td>86.8</td>
</tr>
</tbody>
</table>

Resolution of Enthesitis

<table>
<thead>
<tr>
<th>Week 52</th>
<th>Week 104</th>
<th>Week 156</th>
</tr>
</thead>
<tbody>
<tr>
<td>74.8</td>
<td>74.5</td>
<td>74.8</td>
</tr>
<tr>
<td>75.6</td>
<td>80.3</td>
<td>76.7</td>
</tr>
</tbody>
</table>

Secukinumab 10 mg/kg i.v. → 150 mg s.c.
(Dactylitis: N = 83)
(Enthesitis: N = 99)

Secukinumab 10 mg/kg i.v. → 75 mg s.c.
(Dactylitis: N = 77)
(Enthesitis: N = 91)


Αποδρομή Δακτυλίτιδας και Ενθεσίτιδας σε ασθενείς με αυτά τα συμπτώματα κατά την έναρξη
Sustained Improvement in ACR20 Responses with or without co-treatment with methotrexate

*P < 0.0001; †P < 0.001; ‡P < 0.01; §P < 0.05 vs. placebo
Missing values were imputed as nonresponse (nonresponder imputation) up to Week 52

Secukinumab 300 and 150 mg provided Significant and Sustained Improvements in PASI 75 and PASI 90 Through Week 104 (Overall Population)

PASI 75
(NRI data at Week 24; MI data at Week 52 and Week 104)

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab 300 mg</td>
<td>63.4%</td>
<td>79.7%</td>
<td>79.5%</td>
</tr>
<tr>
<td>Secukinumab 150 mg</td>
<td>48.3%</td>
<td>60.1%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>16.3%</td>
<td>9.3%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

PASI 90
(NRI data at Week 24; MI data at Week 52 and Week 104)

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab 300 mg</td>
<td>48.8%</td>
<td>61.2%</td>
<td>69.6%</td>
</tr>
<tr>
<td>Secukinumab 150 mg</td>
<td>32.8%</td>
<td>45.4%</td>
<td>52.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.3%</td>
<td>9.3%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

*P < 0.0001; †P < 0.001; ‡P < 0.01 vs. placebo

P-values at Week 24 adjusted for multiplicity of testing
Data from subjects with psoriasis ≥ 3% body surface area at baseline.

McInnes IB, et al. Poster presentation at the American College of Rheumatology (ACR) 2016 Annual Scientific Meeting, Washington DC, USA. Abstract no. 2757.
A Case of Recalcitrant Psoriatic Arthritis to TNF Inhibitors Improved After Administration of Secukinumab, an IL-17A Inhibitor

Eleftherios Pelechas · Tereza Memi · Paraskevi V. Voulgarı · Alexandros A. Drosos

a Skin involvement while on etanercept. b Marked improvement on week 4 of secukinumab administration. c Significant improvement on week 36 of secukinumab administration
Conclusions

• spAs are diseases which increase morbidity and mortality
• sPAs decrease drastically the quality of life
• Early detection and referral the patients to the specialist is important in decreasing disease progression
• Criteria for early identification of sPA cases are available
• Criteria for measuring disease activity are available and helpful in evaluating the efficacy of drugs used for treatment of spAs
• Anti-TNF agents, moAbs to P40 subunit of IL-12 and IL-23 and moAbs to IL-17 are important therapeutic agents in our era.